SCIENTIFIC ABSTRACT

Although it has been well established experimentally that the transfer of sensitized T lymphocytes can mediate potent antitumor effects, extrapolating the principles of adoptive immunotherapy obtained from animal studies to clinical therapy will require the development of innovative techniques to isolate and propagate antitumor effector T cells from cancer patients. Toward this end, we have established culture methods whereby cells from tumor-draining or tumor primed lymph nodes (LN) can be sensitized to acquire therapeutic efficacy. Since these cells do not demonstrate overt antitumor reactivity before culture, they are functionally referred to as "pre-effector" cells. One method to generate antitumor effector T cells involves the sequential activation of pre-effector LN cells with anti-CD3 mAb followed by expansion in low concentrations of IL-2. Animal experiments have demonstrated that the antitumor reactivity of these anti-CD3/IL-2 activated cells are exquisitely tumor-specific and mediate the regression of established tumor in adoptive immunotherapy.

A major obstacle which confronts the clinical application of adoptive immunotherapy is the relatively weak immunogenicity of human cancers which hampers the induction of sensitized pre-effector cells. Recent observations in animal studies indicate the tumors can be genetically altered to enhance the host immune response against native or parental tumor antigens. We found that the transfection of the poorly immunogenic B16BL6 murine melanoma tumor with the GM-CSF gene resulted in the sensitization of immune lymphoid cells when inoculated into the syngeneic host. Draining LN cells removed from these animals and activated by the anti-CD3/IL-2 culture procedure generated potent therapeutic effector cells which mediated the adoptive immunotherapy of established metastatic parental tumors. More importantly, these activated cells were more potent in their therapeutic efficacy compared to similarly derived cells utilizing standard bacterial immune adjuvants. These observations provide the rationale for this clinical protocol to examine autologous tumor cells modified with the GM-CSF gene, which will be utilized as a vaccine to induce pre-effector LN cells in patients with advanced cancers. Human cancers have been postulated to be poorly immunogenic based upon their spontaneous origins. These vaccine-primed LN cells will be activated by the anti-CD3/IL-2 method and subsequently transferred intravenously to patients along with the concomitant administration of IL-2 (360,000 IU/kg q8h x 5 days) to support their survival/function in vivo.

The specific aims of the protocol are: 1) To assess the feasibility and toxicity of adoptive T cell immunotherapy of cancer with anti-CD3/IL-2 activated LN cells that are primed in vivo with IL-4 modified autologous tumor cells, 2) To evaluate the antitumor efficacy and in vivo immunological reactivity of patients receiving adoptively transferred T cells, and 3) To investigate the in vitro immunological reactivities of the activated T cells that might correlate with their in vivo antitumor function.